THE LOCAL CIRCULATION OF THE LIVING BRAIN; VALUES IN THE UNANESTHETIZED AND ANESTHETIZED CAT

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The nitrous oxide technique for measurement of cerebral blood flow yields average values of flow for the brain as a whole, but no information about the local blood flow in the many components of that organ. Counts of capillary density provide information related to the vascular needs in these localized regions of the brain, but speculation based upon capillary density data may be more closely related to blood volume than blood flow and need not reflect the changes in local circulation associated with functional activity, the action of drugs or other physiological and pathological variables. Thermoelectric techniques which have been used for this purpose have not given quantitative results and are associated with tissue injury at the site of measurement.

The principles of inert gas exchange in tissues have been employed in the development of a method for the measurement of the local blood flow *in vivo* in specific structures and without tissue damage (Fed. Proc. *14*, 85, 1955). The tissue concentrations of a biologically inert gas abruptly introduced into the arterial blood depend upon the gas solubility in tissue and blood, the history of the gas concentration in the arterial blood, and the tissue circulation. Since all but the last of these can be determined experimentally, the local blood flow can be calculated. The variable arterial concentration of a radioactive gas (CF_3I^{131}) is monitored by means of a scintillation counter while the gas, dissolved in Tyrode's solution, is injected intravenously. The concentrations of the gas achieved in the various regions of the brain at exactly one minute after the start of the injection are measured densitometrically from radioautographs of frozen brain slices, and rate of blood flow per gram of tissue is calculated for specific structures.

The normal values for the local cerebral blood flow in the cat were obtained from a series of experiments performed on ten conscious but restrained cats which were rendered reasonably cooperative by petting. In addition, a similar series of eleven cats under thiopental anesthesia were studied. Both groups were prepared under vinethene anesthesia. After infiltration of the operative sites with procaine to prevent discomfort, the con-

scious cats were restrained by moulded sand bags converted into fairly rigid casts by evacuation of air. An hour was allowed for the vinethene to be completely eliminated before the measurements were begun in both groups. In the anesthetized group, a switch to intravenous thiopental anesthesia was made as soon as feasible, and the depth maintained at the time of measurement was that associated with a feeble corneal reflex.

The blood flow of 28 structures in the central nervous system were studied in both the conscious and the anesthetized series of cats. Representative means values from the series of conscious cats are listed in the order of decreasing flow in Table I.

TABLE I

BLOOD FLOW CC/GM/MIN					
	Mean	Std. Error		Mean	Std. Error
Inferior Colliculus	1.80	±0.11	Caudate	1.10	±0.08
Sensory-Motor Cortex	1.38	±0.12	Thalamus	1.03	±0.05
Auditory Cortex	1.30	±0.05	Association Cortex	0.88	±0.04
Visual Cortex	1.25	±0.06	Cerebellar Nuclei	0.87	±0.07
Medial Geniculate	1.22	±0.04	Cerebellar White Matter	0.24	±0.01
Lateral Geniculate	1.21	±0.08	Cerebral White Matter	0.23	±0.02
Superior Colliculus	1.15	±0.07	Spinal Cord White Matter	0.14	±0.02

It is apparent from the data in Table I that considerably lower values of blood flow were observed in the white matter of the brain and spinal cord than in the gray matter. For example, the highest value obtained in white matter was 0.27 cc/gm/min in the optic tract while the lowest rate of flow in gray matter was 0.63 cc/gm/min in the spinal cord. It is of interest that the values observed in the primary sensory and motor areas of the cerebral cortex greatly exceeded those of other cortical areas with less well-defined function and were surpassed only by that of the inferior colliculus.

In 12 of the 28 structures considered, thiopental significantly reduced the

TABLE II

REDUCTION IN LOCAL BLOOD FLOW DURING THIOPENTAL ANESTHESIA (%)			
Inferior Colliculus	22	Thalamus	31
Sensory-Motor Cortex	53	Association Cortex	24
Auditory Cortex	45	Pontine Gray Matter	31
Visual Cortex	38	Hypothalamus	35
Medial Geniculate	34	Cerebellar Nuclei	29
Lateral Geniculate	35	Basal Ganglia & Amygdala	23

local blood flow. In no case was blood flow increased by thiopental anesthesia. Those structures showing a statistically significant ($p < 0.05$) reduction in local blood flow by thiopental are listed in Table II. The remaining 16 structures studied but not listed in Table II revealed no significant changes with thiopental anesthesia.

Those areas primarily associated with sensory and motor function are most markedly affected by thiopental. It is unlikely that the marked effect in these areas is related to their initial high rates of flow in view of the relatively small reduction observed in the even more rapidly perfused inferior colliculus. Furthermore, whereas local blood flow varied significantly among the various cortical areas in the conscious cat, theiopental anesthesia reduced them all to a relatively uniform level. If the local blood flow of the brain is regulated by the local metabolic rate, then it appears that the most prominent effect of thiopental anesthesia is a reduction in the rate of metabolism and possibly in neuronal activity of the primary cortical areas.

H. H. JASPER: We are all very much impressed with the beautiful, well-controlled study that makes it possible to get in quantitative terms the rate of blood flow in these various nuclear structures of the brain. I think this is a magnificent achievement from the technical point of view. I remember when we used to try to do it with thermocouples. We were impressed with the sensitivity of the local areas of the brain in relation to their function, so that the blood flow reflected the activity in the occipital lobe with stimulation by light or epileptiform disturbances, of course, increasing this effect very markedly; but, of course, these measurements were not quantitative. However, some of them were made by Dr. Penfield on man and I think the authors would hesitate to apply their technic to the human subject. That is one limitation.

I am a little puzzled by some of the results. When I first heard this work, we were interested to know why the geniculate and inferior collicular systems seemed to have such good blood flow. I wondered if they did not have a noisy laboratory. I would like to have them comment on that. Maybe these Geiger counters produce a little stimulation of the auditory system, give an increased blood flow in it.

There is one difficulty, that of interpretation. It seems to me that the changes with function would occur most clearly when the reserve was small, in areas where there is little reserve. I am very much surprised that you do not find greater changes in the brainstem and in the hypothalamus, areas which we would think would be very sensitive to changes in blood flow, some of which are supposed to have something to do with regulating it, as far as I understand. This is puzzling. Is it because the reserve here in relation to function is so great as a protective condition in the brain that under the conditions of your experiment, anesthesia does not seem to make any difference?

I would think hypothalamic areas, however, in relation to function would be more sensitive. Certainly the electrographic pictures of changes in discharge of cells in the brainstem as a function of levels of anesthesia would suggest that you would get great differences, because the brainstem is extraordinarily sensitive to anesthetics.

We have a remarkably interesting tool which is like all new technics; it has given us a wealth of information, much of which is hard to interpret at first.

KNOX FINLEY: My own work on the anatomy of circulation within the central nervous system has been limited to injection techniques, by use of a combination of gelatin and india ink injection material. The technique was used in the monkey and cat, it being necessary to kill the animal by injection technique in order to obtain a perfect injection of the capillary bed of the entire nervous system, including the spinal cord.

Clearly this technique is anatomical and does not apply itself well to physiological variations. It is a technique that can be applied to certain pathological conditions. In poliomyelitis, for example, it could be demonstrated that the capillaries dilate in the inflamed areas. The india ink particles actually diapedese out into the surrounding parenchyma. This technique offered an accurate method of determining capillary density in all regions of the central nervous system. These results are of interest in relation to the findings of the authors today. It has been shown that the fourth layer of calcarine cortex has the richest bed of capillaries within the cerebral cortex.

I can confirm the authors' findings through their own studies that the lateral geniculate body of the inferior and superior colliculi have a rich capillary supply.

The authors found that the hypothalamus as a whole was not as richly supplied as several other areas of the central nervous system. However, there are two important small regions in the hypothalamus, the supraoptic and periventricular nuclei, which have the richest capillary beds of the entire nervous system, the supraoptic nucleus almost double any other region. Of course, the important advance in the use of this technique of using radioactive inert gas is its applicability to function; for here we have a method that will go beyond the anatomical approach to study functional variation of capillary supply in different parts of the brain.

A. GEIGER: It is unnecessary to say that those of us who deal with brain metabolism are extremely glad to see such an elegant method which makes it possible to compare the blood flow rate in different parts of the brain. However, I want to make a remark as to the effect of anesthetic drugs. We found that different barbiturates (and other anesthetic drugs) have very different effects on cerebral blood flow. Some decrease and some increase the cerebral vascular resistance.

I want to ask if the essayist considered the effect of different anesthetics on the distribution of the blood flow.

W. M. LANDAU: In regard to clinical applications, we would certainly agree that even in schizophrenics we doubt if the method would ever apply. It might reasonably apply to neuro-surgical procedures where the surgeon could quickly scoop out a portion of brain tissue instantaneously, as we were able to decapitate the animals. The gas could be administered clinically intravenously or by inhalation.

Dr. Jasper hit on a trouble that worried us, because our scintillation counter apparatus did indeed make a loud clicking noise and particularly during the critical portion of the experiments. We did several series of experiments to try to control this. None of them was large enough to present statistical results. We did a series of about six cats in which the auditory system was destroyed peripherally a month before the experiments, and in all of these the inferior colliculi still stood out like bullets in the radio-autographs. We did a series in which paraffin was placed in the external ear before the experiment was begun and we also covered the eyes of many of the anesthetized cats, in order to cut down on sensory input. Nevertheless, there was always some evidence of high circulation in auditory-visual structures. We have not sufficient evidence to be sure that such procedures may not cut down the auditory-visual circulation somewhat, but they certainly do not bring it down to that of neighboring tissue.

I think probably the phylogenetic age and physiologically critical nature of the brainstem structures may account for their relative intensitivity to the insult of anesthesia. Another possibility is that this brainstem substance contains a large proportion of conducing axonal issue. It may not contain the cellular volume that other gray tissues do.

Of course, we recognize that this is a rather secondhand way of determining physiological activity; it is rather like trying to measure what a factory does by measuring the intake of water and the output of sewage. This is a problem in plumbing and only secondary inferences can be made regarding function. We would not suggest that this

is a substitute for electrical recording in terms of easy evaluation of what is going on.

In answer to Dr. Geiger, we have not studied different anesthetics, if I understood his question correctly. The blood pressure at the time of the experiment was similar in range in both the anesthetized and unanesthetized series.